REMARKS

Claims 1, 2, 5-9, 12-15, 24, 25, 27, and 28 were pending in this application. Claims 2, 5, 9, 12, 27 and 28 have been amended. Eight paragraphs of the specification have been amended to correct typographical errors and references to certain tables therein. Support for the claim and specification amendments are discussed below as necessary.

No new matter is introduced by the foregoing amendments. After entry of this amendment, **claims 1, 2, 5-9, 12-15, 24, 25, 27, and 28 are pending in this application.** Consideration of the pending claims is requested.

Restriction Requirement

Applicants thank the Examiner for "withdrawing" the restriction requirement. However, to ensure that Applicants receive the protections afforded by 35 U.S.C. §121, Applicants ask the Examiner to issue a modified restriction requirement that formally recognizes the elected "Group comprising a single B-cell epitope derived from CD86" (Office action at page 2) and one or more additional groups drawn to the now-canceled subject matter of the first-examined claim set (see, Preliminary Amendment, mailed June 19, 2001).

For example, Applicants suggest Groups such as the following (which refer to the list of claims in the foregoing Preliminary Amendment):

I	Claims 1, 2, 5-9, 12-15, 24, 25, drawn to methods and compositions comprising a B-cell epitope derived from CD86.
II	Claims 1-3, 6-10, 14, 15, 24, 25, drawn to methods and compositions comprising a B-cell epitope derived from CD40.
III	Claims 1, 2, 6-9, 14, 15, 24, 25, drawn to methods and compositions comprising a B-cell epitope derived from CD80.
IV	Claims 1, 2, 4, 6-9, 11, 14, 15, 24, 25, drawn to methods and compositions comprising a B-cell epitope derived from VCAM.
V	Claims 16-18, drawn to antibodies capable of distinguishing between porcine polypeptides and the homologous polypeptides of the mammal receiving a xenograft.
VI	Claims 19, drawn to a method of monitoring an immune state of a mammalian recipient of a xenograft.
VII	Claims 20-23, 26 drawn to a method of treating a mammal prior to receiving a xenograft

Alternatively, if the Examiner intends the limitation to "a B-cell epitope from porcine CD86" (Office action at page 2) to be a species election, where other species (*e.g.*, CD40, CD80, VCAM, and/or non-porcine CD68) will be recombined after a generic claim is found to be allowable, Applicants request that the Examiner explicitly state this in the next Office action.

Information Disclosure Statement

Applicants thank the Examiner for acknowledging the Information Disclosure Statement, filed on June 19, 2001.

Amendments to Specification

The legends of Figures 21, 23, and 25 (on pages 18 and 19) have been amended to remove reference to "underlined sequences [of] peptides identified in [specified] table[s]." The amended figure legends more accurately describe the corresponding figures, which do not contain underlined sequences. In addition, the word "sequence" in each figure legend has been made plural, to correct an inadvertent and obvious typographical error.

The legends of Figures 22, 24, and 26 refer to tables 1, 2, and 3, respectively. The corresponding tables, which can be identified at least by the peptides underlined in the relevant figure, are shown on pages 38-40 of the specification. Pages 38-40 have been amended to clearly identify the table numbers for the respective tables. In making these amendments, it was recognized that two different tables in the specification were inadvertently referred to as "Table 1" (see, pages 23 and 39). Thus, by virtue of amendments herein, the table on page 39 is now named "Table 4" and a corresponding reference to this table (on page 18 of the specification) has been amended accordingly.

The legend of Figure 26 has been amended to replace "human CD86" with "porcine CD86." Comparison of Figures 25 and 26 clearly shows that the amino acid sequence shown in Figure 26 corresponds with the porcine "B7-2" (aka CD86) sequence (not the human sequence).

Claim Rejections under 35 U.S.C. §112, second paragraph:

Claims 5 and 12 have been rejected under 35 U.S.C. §112, second paragraph allegedly as being indefinite for reliance upon a figure. Claims 5 and 12 have been amended to replace the reference to Figure 26 with specific residues of the porcine CD86 amino acid sequence set forth in SEQ ID NO: 14. Support for the particular residues of SEQ ID NO: 14 recited in amended claims 5 and 12 is found, for instance, in Table 1 (at specification page 23).

Claims 2 and 9 have been rejected under 35 U.S.C. §112, second paragraph because the phrase "'derived from' CD86" allegedly is indefinite. Applicants traverse this rejection. Nevertheless to further prosecution of the application, claims 2 and 9 have been amended to replace the phrase "derived from" with the phrase "at least 9 contiguous amino acids of a porcine CD86." These amendments are supported, for instance, at page 13, line 26 of the specification.

In view of the amendments of claims 2 and 9, Applicants request that this rejection be withdrawn.

Claim Rejections under 35 U.S.C. §103(a):

Claims 1, 2, 5-9, 12-15, 27 and 28 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious in light of Etlinger (EP 429,816) in view of Maher *et al.* (*J. Immunol.*, 11:3838-3844, 1996) ("Maher"). Applicants traverse this rejection for the reasons detailed below.

To support an obviousness rejection, the burden is on the Office to establish a *prima facie* case of obviousness (MPEP §2142). To do so, the three basic criteria set forth in MPEP §2142 must be met:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Importantly, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and can not be based on Applicants' disclosure (MPEP §2142, citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)).

Neither Etlinger nor Maher, nor a combination thereof, teaches all of the elements of the rejected claims. For example, none of the references either alone or in combination teach (i) a "method of improving tolerance to a xenograft comprising . . .an immunogen comprising . . . at least one porcine polypeptide B-cell epitope . . . capable of mediating rejection of said xenograft," or (ii) a composition comprising "at least one . . . B-cell epitope compris[ing] a porcine epitope involved in mediating xenograft rejection." The foregoing elements are limitations of each of the claimed methods (*i.e.*, claims 1, 2, 5, 6, 24, and 27) or claimed compositions (*i.e.*, claims 7-9, 12-15, 25, and 28), respectively.

The Office action describes Etlinger as teaching "inducing a humoral response comprising . . . an antigen which comprises a B-cell epitope linked to . . . a T-cell helper epitope." The Office, then, admits that Etlinger "does not teach a vaccine comprising a B cell epitope of porcine CD86 linked to a tetanus toxoid, nor a method for improving tolerance to a xenograph." Applicants note that Etlinger does not teach composition comprising a porcine polypeptide B-cell epitope of any kind (such as, a porcine CD86 epitope) linked to any T-cell epitope (such as, a tetanus toxoid). Thus, Etlinger fails to teach the claimed methods at all and further fails to teach a composition comprising a "at least one . . . B-cell epitope compris[ing] a **porcine epitope involved in mediating xenograft rejection**."

To allegedly make up for the deficiencies in Etlinger, the Office cites Maher and, through a series of mostly unsupported assumptions, describes an alleged biological mechanism that may (or may not) be affected in operation of Applicants' claimed method. This putative biological mechanism standing alone is irrelevant to the determination of obviousness. At best, a biological mechanism may present an invitation to try to exploit the mechanism for a patentable purpose; however, "obvious to try" is not a proper basis for an obviousness rejection (MPEP §2143.02). The three basic criterion of obviousness stated above must be determined with regard to the **claimed** methods and compositions – not an unclaimed biological mechanism.

Maher clearly does not describe any immunogenic compositions (such as those recited in claims 7-9, 12-15, 25, and 28); therefore, Maher can not and does not make up for the

deficiencies in Etlinger, at least, with regard to the compositions recited in claims 7 claims 7-9, 12-15, 25, and 28. Moreover, Maher does not teach a method of improving tolerance to a xenograph involving an immunogen of any kind. Thus, Maher can not and does not make up for the deficiencies in Etlinger with regard to the methods recited in claims 1, 2, 5, 6, 24, and 27.

Even if the biological mechanism explored by Maher was relevant to an obviousness determination, the Office has made unsupported fact assumptions relating to this mechanism, which are impermissible (see, MPEP 2144.03). Moreover, at least some of the unsupported assumptions are factually incorrect, as discussed below. Thus, this rejection is not properly supported by Maher and this reference should be withdrawn or an accurate explanation of its support for this rejection provided.

The Office contends that Maher teaches "**porcine endothelial cells** interact with human T-cell CD28 providing a co-stimulatory response that could be blocked by anti-CD28 antibodies" (Office action at page 4; emphasis added). Thereafter, the Office assumes that "[i]t flows logically . . . that if antibodies to CD28 can block the interaction between the **CD86** . . . and the CD28 of human T-cells, then antibodies to porcine CD86 can also block the interaction between CD86 . . .and CD28 . . . " (Office action at page 4; emphasis added). No where does Maher teach that an interaction between **porcine CD86** and human T-cell CD28 can be blocked by antibodies of any kind. The Office apparently further assumes that because CD86 is a CD28 ligand, the interaction between porcine endothelial cells and human T-cell CD28 (as described by Maher) must be mediated by CD86. However, CD28 has other ligands, including CD80 (see, for example, June *et al.*, *Immunol Today*, 15:321, 1994), which could mediate binding between porcine endothelial cells and human T-cell CD28. Hence, even if the Office properly made "logical" assumptions (which is not conceded), the basic premises are incorrect; therefore, the Office's reliance on Maher is fatally flawed. Accordingly, Maher can not (and does not) make up for the deficiencies in Etlinger.

Based on all of the foregoing arguments, Applicants request that this rejection be withdrawn.

Claims 1, 2, 5-9, 12-15, 24, 25, 27 and 28 have be have been rejected under 35 U.S.C. §103(a) as allegedly being obvious in light of Etlinger and Maher as applied to claims 1, 2, 5-9, 12-15, 27 and 28 (above), and further in view of Muller *et al.* (WO 97/11971) ("Muller"). Applicants traverse this rejection for the reasons stated below.

As discussed above, Etlinger fails to teach the claimed methods at all, and further fails to teach a composition comprising a "at least one . . . B-cell epitope compris[ing] a porcine epitope involved in mediating xenograft rejection." Maher does not teach any immunogenic compositions at all and, therefore, can not (and does not) make up for deficiencies in Etlinger with respect to the rejected composition claims (*i.e.*, claims 7-9, 12-15, 25, and 28). Maher also does not teach a method of improving tolerance to a xenograph involving an immunogen of any kind and, therefore, can not (and does not) make up for deficiencies in Etlinger with respect to the rejected method claims (*i.e.*, 1, 2, 5, 6, 24, and 27). With regard to Maher, the Offices has also improperly assumed facts not supported by evidence and such assumptions are incorrect; hence, for at least two reasons, Maher does not properly supported either of the obviousness rejections set forth in the Office action.

Muller does not make up for the deficiencies in either or both of Etlinger and Maher. Muller teaches antibodies (not immunogens) administered to treat xenograft rejection. As explained in the specification (at page 11, lines 9-24), antibody treatment for this purpose has numerous failings that are solved by the presently claims methods and compositions. Thus, Etlinger, Maher and Muller, either alone or in combination, fail to teach the specific immunogens recited in the rejected claims, and can not (and do not) support this obviousness rejection. Accordingly, Applicants request that this rejection be withdrawn.

Additional Amendments

The claim dependencies of claims 27 and 28 have been amended for proper antecedent basis of these claims.

CONCLUSION

It is respectfully submitted that the present claims are in a condition for allowance. If any issues remain, the Examiner is requested to contact the undersigned attorney prior to issuance of the next Office action in order to arrange a telephone interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution and allowance of the claims.

Respectfully submitted,

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